BEST

Board on Environmental Studies and Toxicology

# Committee to Review EPA's Draft IRIS Assessment of Formaldehyde

**Board on Environmental Studies and Toxicology**

**Division on Earth and Life Studies**

**National Research Council**

**The information presented herein was the product of the Committee's work; however, the interpretation of the information is that of one committee member (Ivan Rusyn) and does not reflect the position of the Academies**

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# Committee

**Jonathan Samet**, (Chair), University of Southern California, Los Angeles
**Andrew Olshan**, (Vice-Chair), University of North Carolina, Chapel Hill
**A. John Bailer**, Miami University, Oxford, OH
**Sandra Baird**, Massachusetts Department of Environmental Protection, Boston
**Harvey Checkoway**, University of Washington School of Public Health and Community Medicine, Seattle
**Richard Corley**, Pacific Northwest National Laboratory, Richland, WA
**David Dorman**, North Carolina State University, Raleigh
**Charles Hobbs**, Lovelace Respiratory Research Institute, Albuquerque, NM
**Michael Laiosa**, University of Wisconsin, Milwaukee
**Ivan Rusyn**, University of North Carolina, Chapel Hill
**Mary Alice Smith**, University of Georgia, Athens
**Leslie Stayner**, University of Illinois, Chicago
**Helen Suh**, Harvard School of Public Health, Boston, MA
**Yiliang Zhu**, University of South Florida, Tampa
**Patrick Zweidler-Mckay**, The University of Texas M. D. Anderson Cancer Center, Houston

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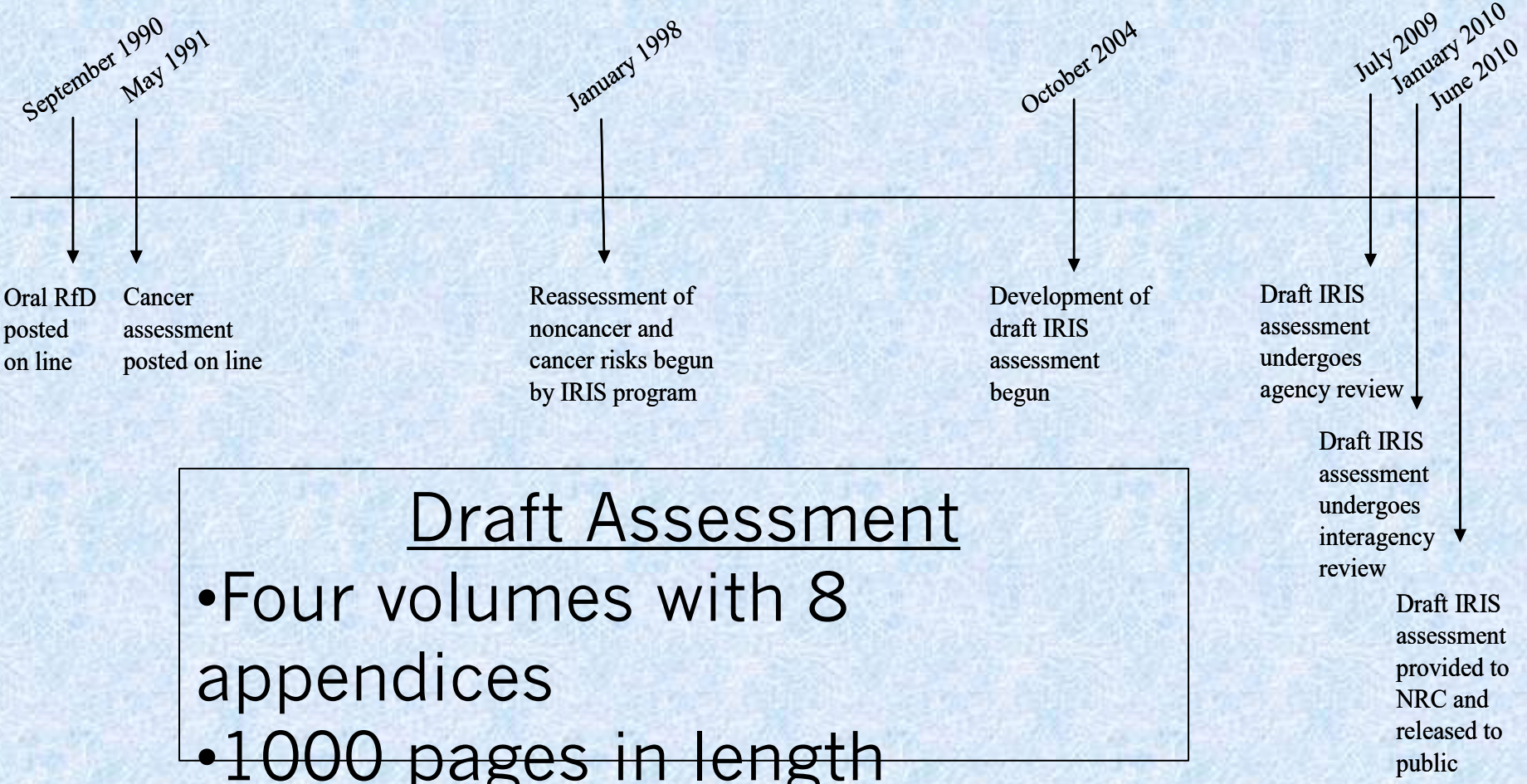
# Committee's Approach to Its Task

- The committee did ***not*** perform its own assessment.
- Thus, it did ***not*** conduct its own literature searches, review all relevant evidence, systematically formulate its own conclusions regarding causality, or recommend values for the RfC and unit risk.
- The committee reviewed the draft IRIS assessment and key literature and determined whether EPA's conclusions were supported on the basis of that assessment and the literature reviewed.

# History of EPA Formaldehyde Assessment




## Draft Assessment

- Four volumes with 8 appendices
- 1000 pages in length

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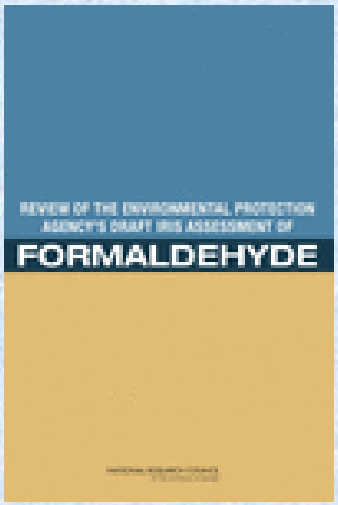
# Overview of the Report

- Chapter 7: Conclusions and Path Forward

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## A Roadmap for Revision

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# General Conclusions on Assessment

- General problems identified by present committee are not unique to the formaldehyde assessment. Previous BEST committees have made similar observations.
- **The draft assessment was not prepared in a consistent fashion and lacks clear links to an underlying framework.**
- **It does not contain sufficient documentation on methods and criteria for identifying evidence from epidemiologic and experimental studies, for critically evaluating individual studies, for assessing the weight of evidence, and for selecting studies for derivation of the RfCs and unit risk estimates.**

# The Path Forward: What needs to be done

The committee concludes that the following six general recommendations are critical to address in the revision of the draft assessment.

- **Rigorous editing is needed to reduce the volume of the text substantially and address the redundancies and inconsistencies; reducing the text could greatly enhance the clarity of the document.**

- **Chapter 1 of the draft assessment needs to discuss more fully the methods used to develop the assessment. The committee is recommending not the addition of long descriptions of EPA guidelines but rather clear concise statements of criteria used to exclude, include, and advance studies for derivation of the RfCs and unit risk estimates.**

# The Path Forward: What needs to be done

- **Standardized evidence tables that provide the methods and results of each study are needed for all health outcomes; if appropriate tables were used, long descriptions of the studies could be moved to an appendix or deleted.**
- **All critical studies need to be thoroughly evaluated for strengths and weaknesses by using uniform approaches; the findings of these evaluations could be summarized in tables to ensure transparency.**
- **The rationales for selection of studies that are used to calculate RfCs and unit risks need to be articulated clearly.**
- **The weight-of-evidence descriptions need to indicate the various determinants of "weight." The reader needs to be able to understand what elements (such as consistency) were emphasized in synthesizing the evidence.**

# Beyond Formaldehyde: Revising the IRIS Process

- The committee is concerned about the persistence of problems encountered with IRIS assessments over the years.
- The committee urges EPA to address the fundamental problems and provides some guidance, most of which focuses on current methods for conducting systematic reviews.
- The following few slides highlight some critical considerations for the development of a scientifically sound IRIS assessment.

"The committee is concerned that little information is provided on what it sees as the most critical step, that is, completion of a draft IRIS assessment. In the flow diagram, six steps are devoted to the review process, and thus the focus of the revision appears to be on the steps after the assessment has been generated."

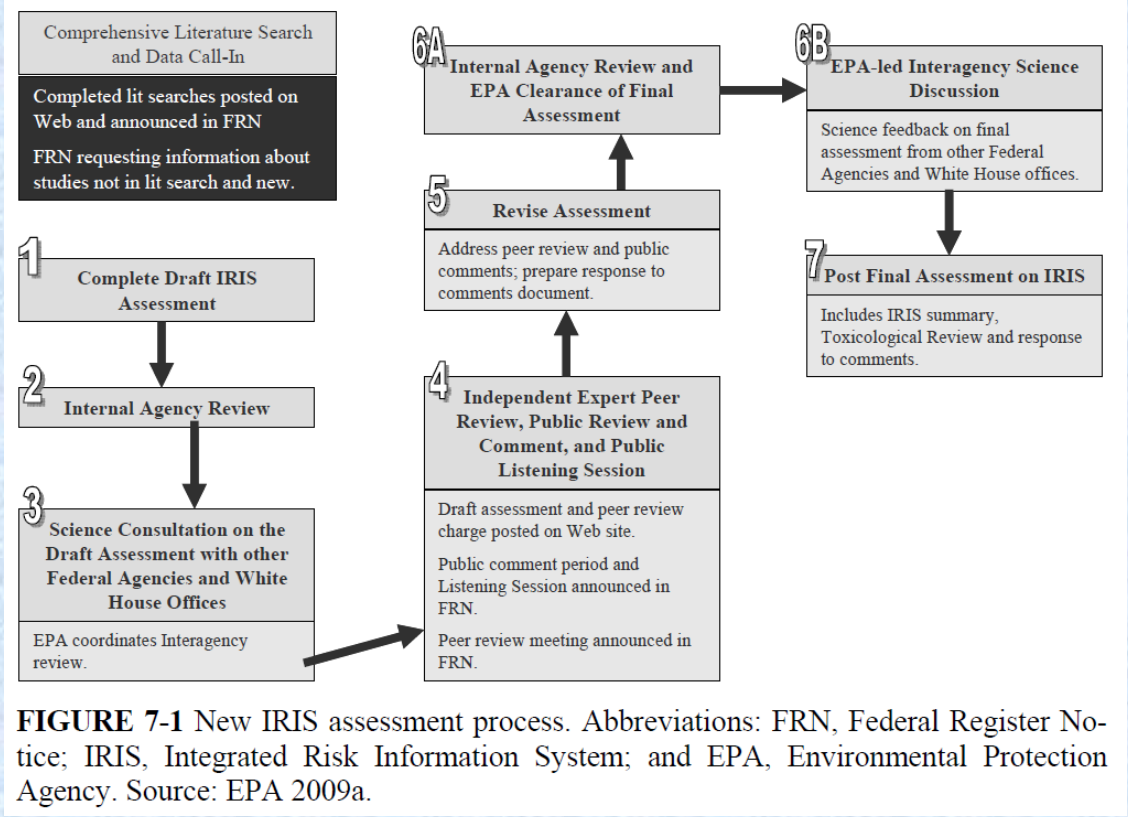


**FIGURE 7-1** New IRIS assessment process. Abbreviations: FRN, Federal Register Notice; IRIS, Integrated Risk Information System; and EPA, Environmental Protection Agency. Source: EPA 2009a.

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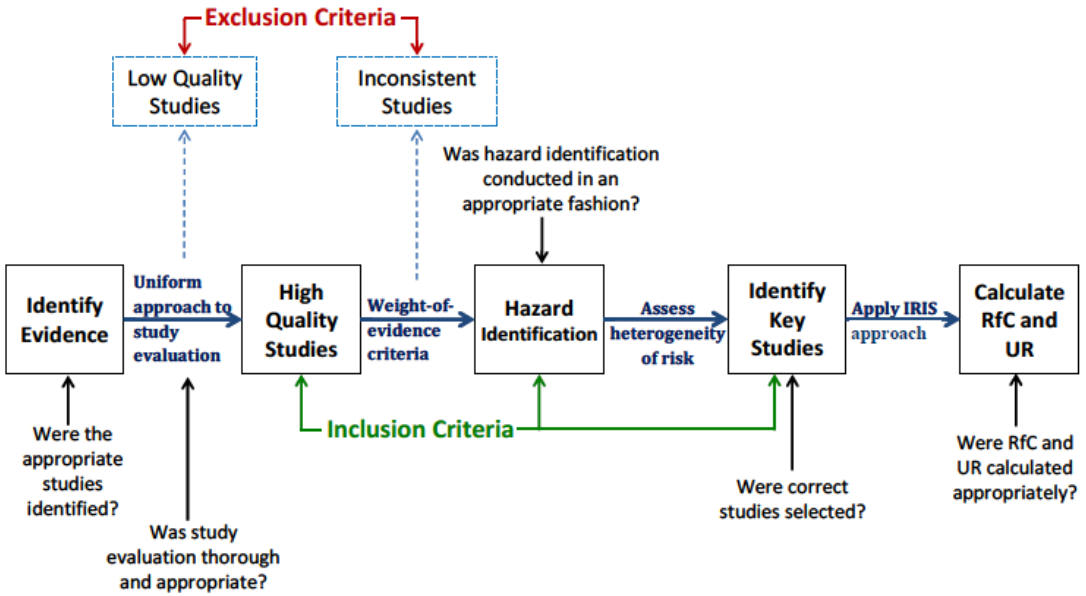



**FIGURE 7-2** Elements of the key steps in the development of a draft IRIS assessment. Abbreviations: IRIS, Integrated Risk Information System; RfC, reference concentration; and UR, unit risk.

**"Neither Chapter 1 nor other chapters of the draft provide a sufficiently detailed description of the approach taken in evaluating individual studies…"**

**"The various EPA guidelines themselves have not been harmonized, and they provide only general guidance. Ultimately, the quality of the studies reviewed and the strength of evidence provided by the studies for deriving RfCs and unit risks need to be clearly presented"**

# Beyond Formaldehyde: Revising the IRIS Process

## General Guidance for the Overall Process

- Elaborate an overall, documented, and quality-controlled process for IRIS assessments.
- Ensure standardization of review and evaluation approaches among contributors and teams of contributors.
- Assess disciplinary structure of teams needed to conduct the assessments.

# Brief Review of Established Best Practices

**TABLE 7-1** Criteria for Determining Causality

| Criterion | Definition |
|---|---|
| Consistency | Persistent association among different studies in different populations |
| Strength of association | Magnitude of the association |
| Specificity | Linkage of specific exposure to specific outcome |
| Temporality | Exposure comes before effect |
| Coherence, plausibility, analogy | Coherence of the various lines of evidence with a causal relationship |
| Biologic gradient | Presence of incre (dose-response r |
| Experiment | Observations fro of exposure (for |

Source: DHHS 2004.

**TABLE 7-2** Hierarchy for Classifying Strength of Causal Inferences on the Basis of Available Evidence

A. Evidence is *sufficient* to infer a causal relationship.

B. Evidence is *suggestive but not sufficient* to infer a causal relationship.

C. Evidence is *inadequate* to infer the presence or absence of a causal relationship (evidence that is sparse, of poor quality, or conflicting).

D. Evidence is *suggestive of no causal relationship*.

Source: DHHS 2004.

# Beyond Formaldehyde: Revising the IRIS Process

**Evidence Identification:**

**Literature Collection and Collation Phase**

- **Select outcomes on the basis of available evidence and understanding of mode of action.**
- **Establish standard protocols for evidence identification.**
- **Develop a template for description of the search approach.**
- **Use a database to capture study information and relevant quantitative data.**

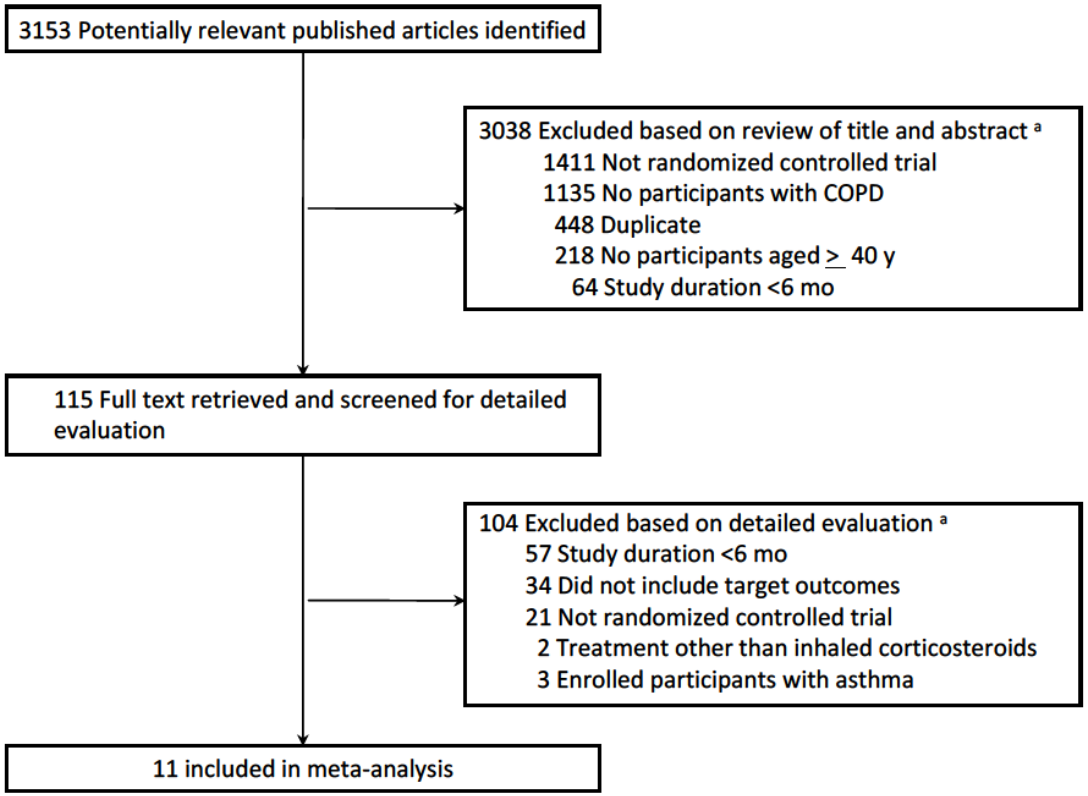



**FIGURE 7-3** Example of an article-selection process. [a]Articles could be excluded for more than one reason; therefore, summed exclusions exceed total. Abbreviation: COPD, chronic obstructive pulmonary disease. Source: Drummond et al. 2008. Reprinted with permission; copyright 2008, American Medical Association.

# Beyond Formaldehyde: Revising the IRIS Process

## Evidence Evaluation: Hazard ID and Dose-Response Modeling

- Standardize the presentation of reviewed studies in tabular or graphic form to capture the key dimensions of study characteristics, weight of evidence, and utility as a basis for deriving reference values and unit risks.
- Develop templates for evidence tables, forest plots, or other displays.
- Establish protocols for review of major types of studies, such as epidemiologic and bioassay

# Beyond Formaldehyde: Revising the IRIS Process

**Weight-of-Evidence Evaluation: Synthesis of Evidence for Hazard ID**

- **Review use of existing weight-of-evidence guidelines.**
- **Standardize approach to using weight-of-evidence guidelines.**
- **Conduct agency workshops on approaches to implementing weight-of-evidence guidelines.**
- **Develop uniform language to describe strength of evidence on noncancer effects.**
- **Expand and harmonize the approach for characterizing uncertainty and variability.**
- **To the extent possible, unify consideration of outcomes around common modes of action rather than considering multiple outcomes separately.**

# Selection of Studies for Derivation of RfCs and Unit Risks

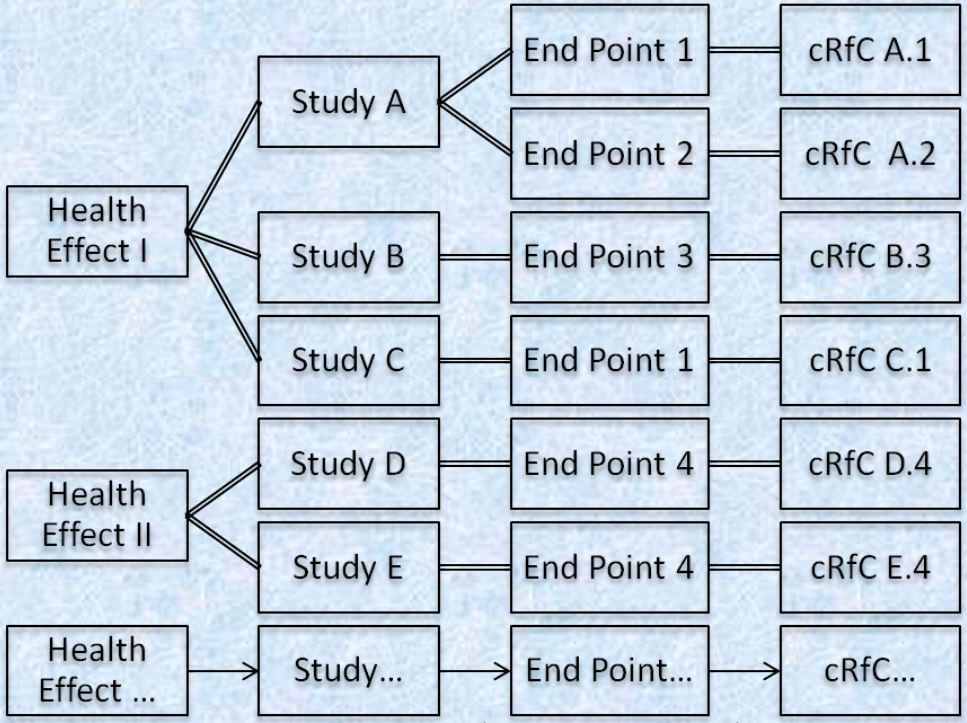
- **Establish clear guidelines for study selection.**
  - ➢ **Balance strengths and weaknesses.**
  - ➢ **Weigh human vs experimental evidence.**
  - ➢ **Determine whether combining estimates among studies is warranted.**

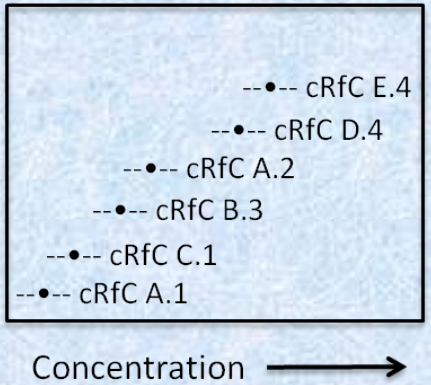
# Beyond Formaldehyde: Revising the IRIS Process

## Calculation of Reference Concentrations and Unit Risks

- Describe and justify assumptions and models used.
- Provide explanation of the risk-estimation modeling processes that are used to develop a unit risk estimate.
- Assess the sensitivity of derived estimates to model assumptions and end points selected.
- Provide adequate documentation for conclusions and estimation of reference values and unit risks.

# Derivation of Reference Concentrations

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# Beyond Formaldehyde: Revising the IRIS Process

- The committee recognizes that revision of the overall approach will involve an extensive effort by EPA staff and others, and **it is not recommending that EPA delay the revision of the formaldehyde assessment to implement a new approach**.

- **However, if the methodologic issues are not addressed, future assessments may still have the same general and avoidable problems that are highlighted in this report.**